(4) providing cells expressing the gene encoding the non-aberrant receptor,

(5) providing to the cells expressing the non-aberrant receptor a natural substance which operates the non-aberrant receptor and does not operate the aberrant receptor,

(6) determining the operation activity in (5), and

(7) comparing the operation activity in step (3) with that of step (6), wherein a similar activity indicates that the subject substance causes the aberrant receptor to operate in a manner similar to the non-aberrant receptor.

REMARKS

In the Official Action dated September 10, 2002, claims 1-14, 16-19, 21-24 and 26-44 are pending, claims 1-13 are withdrawn as being drawn to a non-elected invention and claims 14, 16-19, 21-24 and 26-44 are currently under examination and stand rejected. In the above amendment, claims 14, 16, 17, 21, 24 and 27 are cancelled, without prejudice. Claims 18, 19, 22, 26, 28-31, 33, 35, and 36 have been amended to change dependencies from the cancelled claims to claims 39-44. Claim 44 has been amended to correct a typographical error. No new matter has been added by these amendments. Applicant respectfully requests reconsideration and withdrawal of the outstanding rejections in light of the amendments.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached pages are captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

A petition for an extension of time of three (3) months for responding to the outstanding Office Action and the appropriate fee is enclosed herewith.

Applicant acknowledges the withdrawal of the rejections of claims under 35 U.S.C. §112, paragraph 2.

Claims 14, 16-19, 24, 26-38 stand rejected under 35 U.S.C. 102(b) as being anticipated by Birnbaumer et al., Molecular Endocrinology 8(7): 886-894, 1994, for

reasons of record. Applicant respectfully traverses this rejection. However, in order to expedite examination of this application, claims 14, 16, 17, 21, 24 and 27 have been cancelled. The amendments to the claims obviate this rejection. For example, claims 18, 19, 26-38 have been amended to depend from claims 39-44, which recite that the subject substance comprises a synthetic compound, which substantially fails to operate the non-aberrant receptor. Birnbaumer does not teach the use of a "subject substance comprises a synthetic compound, which substantially fails to operate the non-aberrant receptor" as presently claimed. Thus, Birnbaumer fails to anticipate the invention recited in the above claims.

Applicant respectfully requests reconsideration and withdrawal of this rejection.

Claim 14 stands rejected under 35 U.S.C. 102(b) as being anticipated by Green et al., J. Biol. Chem. 268(31): 23116-23121, 11/5/93, for reasons of record. While Applicant disagrees with the Examiner's position, claim 14 has been cancelled in order to expedite examination of this application. In light of the fact that claim 14 has been cancelled, Applicant respectfully requests reconsideration and withdrawal of this rejection.

Claim 14 stands rejected under 35 U.S.C. 102(b) as being anticipated by Kong et al., J. Biol. Chem. 268(31): 23055-23058, 1993, for reasons of record. While Applicant disagrees with the Examiner's position, claim 14 has been cancelled in order to expedite examination of this application. In light of the fact that claim 14 has been cancelled, Applicant respectfully requests reconsideration and withdrawal of this rejection.

Claims 14, 16-19, 21-24 and 26-38 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Lebrun et al., in view of Choong et al., for reasons cited in the previous Office Actions. Applicant respectfully traverses this rejection.

The rejection as it relates to claims 14, 16, 17, 21, 24 and 27 is mute, since these claims have been cancelled.

Applicant refers the Examiner to previous responses for a complete discussion of Lebrun et al., and Choong, et al.

Applicant respectfully submits that the methods of the present invention would not have been obvious to one of ordinary skill in the art at the time the invention was made. The Examiner has previously stated that

> it would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to substitute the mutated androgen receptor of Choong et al. in the method of Lebrun et al. for the purpose of finding an antibody that would compensate for the androgen receptor mutation. (Underlining added).

The Examiner has argued that one of ordinary skill in the art would look to other type of receptors (e.g., an androgen receptor) to gain information to study a receptor of interest (e.g., an insulin receptor). While this may generally be true, it is well-established law that the mere fact that references can be combined is not enough. There must be a "suggestion or motivation in the reference to do so." The prior art must suggest the desirability of the combination. See MPEP §2143.01 and cases cited therein. Contrary to the Examiner's contention, the references cited by the Examiner simply fail to suggest such a combination. As Applicant has stated in previous responses, the two references each address a different disease and a different receptor. There would be no reason for one of ordinary skill in the art that was interested in studying an insulin receptor mutation to look to an article addressing an androgen insensitivity.

Furthermore, the references cannot support a combination if to do so would render the prior art unusable for its intended purpose. See MPEP §2143.01, §2145 and cases cited therein. The combination of Choong with Lebrun would simply render Lebrun useless. As aforesaid, the two references each address a different disease and a different receptor. To combine the teachings of the two references (where one addresses androgen insensitivity and the other addresses an insulin receptor

mutation) would render the goal of Lebrun, i.e., to study the insulin receptor, unattainable. Thus, the present rejection is not proper.

However, in order to expedite allowance of claims 18, 19, 22, 23, 26, 28-38, Applicant has amended these claims to depend from claims 39-44, which recite that "the subject substance comprises a synthetic compound, which substantially fails to operate the non-aberrant receptor." Lebrun et al., in view of Choong et al. fail to teach or suggest the methods of screening for substances, where the subject substance comprises a synthetic compound, which substantially fails to operate the non-aberrant receptor. The claims, therefore, would not have been obvious to one of ordinary skill in the art based on the teachings of Lebrun et al. and Choong et al.

Furthermore, in the present Office Action, the Examiner has stated that the claims do not include the limitation that the substance to be screened may not an antibody. Thus, the claims as presently amended, exclude antibodies.

Thus, in light of the above amendments to the claims, Applicant respectfully requests reconsideration and withdrawal of this rejection.

Claims 39-44 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Birnbaumer et al., or Green et al., or Kong et al., or Lebrun et al. in view of Choong et al., and further in view of Dower et al., U.S. Patent No. 5,639,603, June 17, 1997. Applicant respectfully traverses this rejection.

The Examiner did not specifically set forth a discussion of each reference, but referred to earlier Office Actions. Applicant therefore refers the Examiner to Applicant's discussions of these references in Applicant's previous responses to those Office Actions. However, Applicant addresses below the comments that the Examiner made on these references in the present Office Action with respect to the citation of those references in the rejections under §102.

In the present Office Action, the Examiner cites the use of dDAVP in Birnbaumer to activate a mutant type-2 vasopressin receptor in dogs as evidence that the teachings of Birnbaumer et al. teach the presently claimed methods. Applicant respectfully submits that the Examiner's discussion of Birnbaumer's dog study is not relevant to the present invention. This study merely shows that the symptoms of congenital nephrogenic diabetes insipidus (CNDI) could be relieved by frequent administration of deamino[8-D-Arg]vasopressin (dAVP), which is a V2R-selective agonist (see pages 890-892). This result shows the reduced affinity of the receptor for AVP. This result, however, does not show the ability of a compound (dAVP) to operate the aberrant receptor in a manner similar to a non-aberrant receptor. The Examiner, in fact, admits that Birnbaumer et al. did not find a compound that caused the mutant type-2 vasopressin receptor to operate in a manner similar to the wild-type receptor, as presently claimed.

Furthermore, there is no disclosure in Birnbaumer relating to the affinity of dog mutant type-2 vasopressin receptor for dAVP. Birnbaumer et al., simply do not teach or suggest the ability of dAVP to operate the aberrant receptor in a manner similar to a non-aberrant receptor.

In the present Office Action, the Examiner cites Green et al. as teaching "screening for compounds to determine the effect of the compound on activity of the receptor." The Examiner states that Green et al. found that dopamine had the same effect on both the wild type and mutant receptor. Applicant respectfully submits that Green did not test compounds to determine their effect on the activity of the mutant and wild-type receptors, but rather, merely tested their binding affinities for each of the receptors. In fact, dopamine is not a ligand for the β2-adrenergic receptor, which was the type of receptor of interest in Green. Furthermore, in Table 1 of Green, dopamine is used an amount which is on the order of μM, which is about 1000 times greater than that of epinephrine, the ligand of the β2-adrenergic receptor. Therefore, Applicant respectfully submits that the Examiner's finding that dopamine had the same effect on both the wild type and mutant receptor is not accurate and does not render the presently claimed invention obvious.

In the present Office Action, the Examiner cites Kong et al. as teaching the methods of the present invention. Applicant respectfully disagrees. As stated in previous responses, Kong merely studies the binding affinity of certain agonists to the mutant and wild type receptors, but fails to teach the change in operation activity of the mutated receptor to function like the wild type receptor. It is the Examiner's position that the description at page 23056 and Figure 2, in which COS-7 cells were transfected with either the wild type or D95N mutant, stimulated with forskolin in the presence or absence of opioid agonists, and cAMP formation was measured would have rendered the present methods obvious in view of Dower. Again, as in Green, et al., discussed above, Figure 2 shows the effect of the use of 1 μM of opioid antagonists. Such a high concentration of antagonist is not realistic in this type of experiment and one of ordinary skill in the art would not be motivated to use the teachings of Kong, et al. to obtain the methods of screening that are presently claimed. Thus, the methods of the present invention would not have been obvious in view of Kong.

Lebrun and Choong are discussed in previous responses and above. Neither reference, alone or in combination would have rendered the present invention obvious to one of ordinary skill in the art.

The Examiner admits that Birnbaumer et al., Green et al., Kong et al., Lebrun et al. and Choong et al. do not disclose screening synthetic compounds.

The Examiner cites Dower et al. as teaching that synthetic compounds can be generated and screened to identify and isolate compounds with useful properties. It is the Examiner's position that Dower teaches methods of screening large libraries of synthetic compounds "that could bind to and activate an aberrant receptor". (Underline added). Applicants respectfully disagree with the Examiner's interpretation of Dower. Dower fails to teach the measurement of the operation activity of the receptors of interest.

Applicant respectfully submits that Dower, et al. teach the screening of compounds by measuring the binding of screened compounds to the receptor of interest. For example, the specification summarizes the invention as follows: "In general, the invention provides improved methods for generating and screening molecular libraries in which the individual molecules in the library are tagged with unique, easily decoded identifier tags." Col. 5, line 12-15.

In contrast, the methods of the present invention measure the operation activity of the compounds on the receptor, not just binding. While Dower teaches the screening of libraries of synthetic compounds, it fails to teach the measurement of the effect of the compounds on the activity of the receptor. Dower simply fails to make up for the deficiencies in the other cited references.

Furthermore, there is simply no motivation or suggestion in any of the references to combine the teachings of Birnbaumer et al., or Green et al., or Kong et al., or Lebrun et al. in view of Choong et al., with Dower et al. Birnbaumer et al., or Green et al., or Kong et al., or Lebrun et al. simply fail to teach the desirability of screening large libraries of compounds for binding with their receptors of interest. Thus, there would be no motivation to look to Dower in the first place.

Even if one of ordinary skill in the art were motivated to combine any of Birnbaumer et al., or Green et al., or Kong et al., or Lebrun et al. in view of Choong et al., with Dower et al., the methods of the present invention would not have been obvious from those teachings. At most, Dower would provide for a method of tagging different reactions with a peptide of interest for further identification.

Thus, the methods of the present invention would not have been obvious to one of ordinary skill in the art based upon the teachings of Birnbaumer et al., or Green et al., or Kong et al., or Lebrun et al. in view of Choong et al., and further in view of Dower et al. Applicant respectfully requests reconsideration and withdrawal of this rejection.

In view of the above amendment and discussion, it is respectfully submitted that the present application is in condition for allowance. An early reconsideration and notice of allowance are earnestly solicited. Should the Examiner wish to discuss the above amendment made herein, the undersigned attorney would appreciate the opportunity to do so. Thus the Examiner is hereby invited to call the undersigned, collect at the number shown below.

Respectfully submitted,

Date: March 6, 2003

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Please amend the claims as follows:

Please cancel claim 14, without prejudice.

Please cancel claim 16, without prejudice.

Please cancel claim 17, without prejudice.

18. (twice amended) The screening method according to claim ~~16~~ 40, wherein the aberrant receptor is isolated from a cell which expresses the gene encoding the aberrant receptor.

19. (three times amended) The screening method according to claim ~~16~~ 40, wherein the aberrant receptor is encoded by a gene in the mammal, the method further comprising the step of selecting the receptor by comparing the gene encoding the aberrant receptor, isolated from a cell of the mammal, with a gene encoding the non-aberrant receptor, prepared from a cell of a mammal of the same species that does not carry the aberrant receptor.

Please cancel claim 21, without prejudice.

22. (four times amended) The method according to claim ~~21~~ 42, wherein the aberrant receptor, which has substantially changed affinity for substances, is encoded by a gene in the mammal and is isolated from a cell which expresses the gene encoding the aberrant receptor.

Please cancel claim 24, without prejudice.

26. (twice amended) The method according to claim ~~24~~ 43 wherein the substance normally operates said receptor.

Please cancel claim 27, without prejudice.

28. (amended) The method according to claim ~~14~~ 39, wherein the operation activity is a change in intracellular concentrations of responding substances selected from the group consisting of cAMP, inositol phosphate and calcium ion.

29. (amended) The method according to claim ~~16~~ 40, wherein the operation activity is a change in intracellular concentrations of responding substances selected from the group consisting of cAMP, inositol phosphate and calcium ion.

30. (amended) The method according to claim ~~17~~ 41, wherein the operation activity is a change in intracellular concentrations of responding substances selected from the group consisting of cAMP, inositol phosphate and calcium ion.

31. (amended) The method according to claim ~~18~~ 42, wherein the operation activity is a change in intracellular concentrations of responding substances selected from the group consisting of cAMP, inositol phosphate and calcium ion.

33. (amended) The method according to claim ~~24~~ 43, wherein the operation activity is a change in intracellular concentrations of responding substances selected from the group consisting of cAMP, inositol phosphate and calcium ion.

35. (amended) The method according to claim ~~27~~ 44, wherein the operation activity is a change in intracellular concentrations of responding substances selected from the group consisting of cAMP, inositol phosphate and calcium ion.

36. (amended) The method according to claim ~~21~~ 42, wherein the activity of the signal transduction system of cells is a change in intracellular concentrations of responding substances selected from the group consisting of cAMP, inositol phosphate and calcium ion.

44. (amended) A method of screening for a substance capable of causing an aberrant receptor, which has substantially changed affinity for natural substances that have a natural affinity for a non-aberrant receptor, to operate in a manner similar to a non-aberrant receptor comprising:

(1) providing cells expressing the gene encoding the aberrant receptor,

(2) providing a subject substance to be screened to the cells expressing the aberrant receptor, said subject substance comprising a synthetic compound which substantially fails to operate the non-aberrant receptor,

(3) determining the operation activity of said subject substance on said receptor,

(4) providing cells expressing the gene encoding the non-aberrant receptor,

(5) providing to the cells expressing the non-aberrant receptor a natural substance which operates the non-aberrant receptor and does not operate the aberrant receptor,

(6) determining the operation activity in (5), and

(7) comparing the operation activity in step (3) with that of step (6), wherein a similar activity indicates that the subject substance causes the aberrant receptor to operate in a manner similar to the non-aberrant receptor.